REMARKS/ARGUMENTS

With this amendment, claims 1-4, 6-8 and 16 are pending. Claims 5, 9, 22 and 27 are cancelled without prejudice to subsequent revival. New claims 28 and 29 are added. For convenience, the Examiner's rejections are addressed in the order presented in the August 4, 2003, Office Action.

I. Status of the claims

Claims 5, 9, 22 and 27 are cancelled without prejudice to subsequent revival.

Claim 4 is amended to recite that the antibody is capable of eliciting a cytotoxic response of the malignant cells. Support for this amendment is found throughout the specification, for example at page 22, line 5, and at page 27, lines 12-15. This amendment adds no new matter.

Claims 1 and 16 are amended to recite that the antibody binds to an epitope in the amino terminal extracellular domain of frizzled 5 that is SEQ ID NO:68. Support for this amendment is found throughout the specification, for example at Table II on page 11, and at Figure 8. Claims 1 and 16 are also amended to recite that the antibody inhibits growth of a malignant cell that expresses frizzled 5. Support for this amendment is found throughout the specification, for example at page 22, lines 4-5. These amendments add no new matter.

New claim 28 is directed to a purified antibody for immunotherapy of a malignant cell that overexpresses a frizzled 5 receptor, where the antibody binds to an epitope in the amino terminal extracellular domain of frizzled 5 that is SEQ ID NO:68. Support for this amendment is found throughout the specification, for example at page 18, lines 4-6, and pages 21-22. New claim 29 is directed to a pharmaceutical composition comprising the antibodies of claim 28. Support for this amendment is found throughout the specification, for example at page 22, lines 10-23.

II. Rejections under 35 U.S.C. §112, second paragraph

Claims 1-9 and 27 are rejected as allegedly indefinite, apparently because claim 9 recites frizzled-2 receptor. In order to expedite prosecution, claim 9 is cancelled. This amendment adds no new matter.

Claim 4 is rejected as allegedly indefinite for reciting capable of sensitizing malignant cells expressing the frizzled 5 receptor to a cytotoxic factor. In order to expedite prosecution, claim 4 is amended to recite that the antibody is capable of eliciting a cytotoxic response of the malignant cells, indicating more clearly that the antibody causes the death of the malignant cells.

III. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1-9, 16, 22 and 27 are rejected as allegedly lacking written description under 35 U.S.C. §112, first paragraph. The Office Action points out that the purpose of the written description requirement is to demonstrate to those of skill that the inventors had possession of the claimed invention at the time of filing. The Office Action concedes that the specification adequately describes SEQ ID NO:68, the extracellular portion of the frizzled 5 receptor. In order to expedite prosecution, claims 1 and 16 are amended to recite that the antibody binds to an epitope in an amino terminal extracellular domain that is SEQ ID NO:68.

Claim 5 is also rejected as allegedly lacking written description under 35 U.S.C. §112, first paragraph. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Office Action alleges that a specific wnt that binds to frizzled 5 must be included in the language of claim 5. However, at the time of filing the application, wnt proteins were known to those of skill (including wnt5A), as was their role in binding to frizzled proteins, and their role in activating wnt/fzd signaling pathways through that binding. Claim 5 is dependent on claim 1, and thus, is now drawn to antibodies that bind to SEQ ID NO:68 and that also inhibit wnt binding. Based on the specification and knowledge of wnt proteins at the time of filing, one of skill would have recognized that the inventors were in possession of the claimed invention at the time of filing the application.

IV. Rejections under 35 U.S.C. §103(a)

Claims 1-9, 16, 22, and 27 are rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of Tanaka *et al.*, *PNAS USA* 95:10,164-9; He *et al. Science* 275:1652-2; or Wang *et al.*, *J. Biol. Chem.* 271:4468-76 in view of Campbell, Monoclonal antibody Technology, Chapter 1. According to the Office Action, SEQ ID NO:68, *i.e.*, the extracellular domain of frizzled 5, is the same as the full length frizzled 5 protein disclosed in the references.

To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection. The Office Action has not established a case of *prima facie* obviousness. To establish a case of *prima facie* obviousness, the Examiner must meet three basic criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). M.P.E.P. §§ 706.02(j) and 2143.

According to 35 U.S.C. §103(a), a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." The phrase "at the time the invention was made" ensures that obviousness analysis is performed without the benefit of impermissible hindsight. The Federal Circuit has ruled that

> . . . the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. . . . Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999), citations omitted.

The Federal Circuit recognizes that evidence of a suggestion, teaching or motivation to combine can be found in a number of sources. However, actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *Id.*

The references cited by the Office Action fail to provide a reasonable expectation of success in practicing the invention and fail to provide all the elements of the rejected claims. In addition, the references cited by the Office Action and the arguments put forth within the Office Action fail to provide evidence of a clear and particular showing of a motivation to combine the cited references to arrive at the claimed invention.

The claims are directed to antibodies that bind to the amino terminal extracellular domain of the frizzled 5 receptor, and that inhibit growth of a malignant cell that expresses the frizzled 5 protein. The claimed invention is based, at least in part, on the recognition that frizzled proteins, including frizzled 5, are overexpressed in some cancers, and thus, can be used as tumor specific antigens that can be used to generate immunotherapy agents. The claimed antibodies are immunotherapy agents used to inhibit growth of or kill cancer cells. None of the cited references provide evidence that the frizzled 5 protein is overexpressed in malignant cells or that antibodies directed against frizzled 5 are useful to kill cancer cells that express frizzled 5. Without recognition of the role of frizzled proteins in cancer, antibodies against frizzled proteins would be raised only to function as research tools, not as growth inhibiting immunotherapeutic agents. In addition, none of the cited references disclose the specifically claimed amino terminal extracellular domain of frizzled 5 or antibodies against that domain.

Tanaka *et al.* disclose the cloning of the frizzled 7 gene and report that frizzled 7 is overexpressed in esophageal cancer. Tanaka *et al.* disclose a portion of frizzled 5 amino acid sequence (not the same as SEQ ID NO:68) and further show that expression of frizzled 5 is not correlated with esophageal cancer (see, *e.g.*, Figure 1). Thus, Tanaka *et al.* fail to disclose the claimed amino terminal extracellular frizzled 5 sequence and, in fact teach away from a role for frizzled 5 in cancer. Because of that failure, the disclosure of Tanaka *et al.* also fail to provide evidence of a motivation to identify antibodies directed against frizzled 5 that inhibit proliferation of cancer cells.

He *et al.* disclose a role for frizzled 5 and wnt 5A in development, but do not disclose any role for frizzled 5 in cancer. In addition, He *et al.* cite Wang *et al.* for the frizzled 5 sequence and do not provide any other frizzled 5 sequence or subsequence. Thus, He *et al.* do not provide the claimed frizzled 5 sequence or evidence of a motivation to use that sequence to produce antibodies against frizzled 5 that inhibit proliferation of cancer cells.

Wang *et al.* disclose the full length sequence of frizzled 5 but do not disclose the amino terminal extracellular domain of frizzled 5 or its use to make the claimed antibodies. Therefore, Wang *et al.* do not teach the amino terminal extracellular domain of frizzled 5 as is claimed. Wang *et al.* do not disclose a role for frizzled 5 in cancer and thus do not provide evidence of a motivation to identify antibodies against the amino terminal extracellular domain of frizzled 5 that inhibit proliferation of cancer cells.

Campbell discloses only general methods to make antibodies. Campbell does not disclose or suggest using the amino terminal extracellular domain of frizzled 5 to produce antibodies and does not provide a particular showing of the use of frizzled 5 antibodies as immunotherapeutic agents. Thus, Campbell does not provide evidence of a motivation to combine the cited references to arrive at the claimed invention.

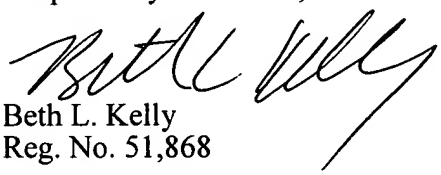
In summary, alone or in combination, the cited references do not disclose all the elements of the claimed invention and do not provide evidence of a motivation for their combination to arrive at the claimed invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Beth L. Kelly
Reg. No. 51,868

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
BLK:blk
60073394 v1